"At risk mental state" clinics for psychosis - An Idea Whose Time Has Come - and Gone!

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Introduction

The idea of early intervention (EI) services for people suffering their first episode of psychosis (FEP) was conceived as a way to improve the long-term outcomes of the illness (Falloon, 1992; Falloon *et al*., 1996). Indeed, the results of EI services, such as the Lambeth Early Onset (LEO) (Craig *et al*., 2004) and OPUS (Hastrup *et al.*, 2013), have been encouraging and led to such services becoming widely established. In a further extension of the idea, specific clinical criteria were proposed to identify people who were at high clinical risk of developing psychosis in the subsequent 1-2 years (Yung *et al*., 1996; Yung *et al.*, 2006). The definition of this pre-psychosis phase in which people manifested the At Risk Mental State (ARMS) (Fusar-Poli *et al*., 2013) was followed by claims that identification of such individuals who were at ultra-high risk (UHR) of developing psychosis, provides a valuable opportunity to prevent a substantial proportion of pre-psychotic individuals from transitioning to clinical psychosis (Yung *et al*., 2005). Subsequently, detection of young people with the ARMS has become a popular prevention strategy (Reddy, 2014) with the creation of ARMS clinics in ~~ma~~many~~jor~~ countries ~~around the world~~ (Addington *et al*., 2008; Cannon *et al*., 2016; Fusar-Poli *et al*., 2013; Yung *et al*., 2006).

ARMS clinics are specialised mental health services for help-seeking people, who are usually aged 14-35 years old and considered to be at UHR of developing psychosis. The stated purpose of these clinics is to reduce, or deter, transitions from the ARMS state to clinical psychosis (Fusar-Poli *et al*., 2013; Green *et al*., 2011). Many studies of ARMS clinics report evidence for their benefits and provide “evidence-based recommendations” or “guidance” for the treatment of such individuals (Killackey and Yung, 2007). However, the strength of such claims has not been established (Morrison *et al*., 2012). The purposes of this article are two-fold. First, we sought to review the robustness of the claims that ARMS clinics have the capacity to prevent transition to psychosis; and second, we aimed to raise the question of whether it may be more beneficial for prevention of psychosis to adopt a public health

approach, which in turn would target risk factors for the illness onset rather than focusing on the ARMS phase.

Defining the At Risk Mental State (ARMS) phase

The ARMS phase is characterised by either 'attenuated' psychotic symptoms, or full-blown psychotic symptoms that are brief and self-limiting (Fusar-Poli *et al*., 2013). It may also manifest as a significant decrease in functioning in the context of a familial (presumed genetic) risk for schizophrenia, or subtle subjective disturbances of cognitive processes, thinking, perception, moods and behaviours (Yung *et al*., 2003; Yung *et al*., 2006). To increase objectivity and diagnostic accuracy of this construct, several scales, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al*., 2005) and the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller *et al*., 2003; Woods *et al*., 2009) have been designed to measure these symptoms with arguably reasonable inter-rater reliability (Loewy *et al*., 2011).

However, it has been reported that as many as 84% of those individuals who were identified as being at risk for the illness using these scales did not develop a psychotic disorder within 2-3 years (i.e., these individuals are normally referred to as "false positives") (Corcoran *et al*., 2010). Even when the diagnosis of the ARMS was made by experienced clinicians, the false-positive rate remained substantially high (47%) (Yung *et al*., 2008). This may suggest that the difficulty in identifying individuals with the ARMS lies in defining the construct. Indeed, it has been shown that the proportion of adolescents who meet criteria for the ARMS varies from 0.9% to 22.6% depending on slight variations in the ARMS criteria (Kelleher *et al*., 2012). Furthermore, attempts to identify specific biological markers of the ARMS phase and predictors of a transition from the ARMS to clinical psychosis have been unsuccessful (Castle, 2012; Wood *et al*., 2013). It has therefore been argued that early

intervention on the basis of the screening criteria for subclinical psychosis is not feasible in the general population (van Os, 2005).

Services for the ARMS phase create useful pathways to care – but for whom?

Most clinics for young people who meet criteria for the ARMS, accept referrals via a wide range of means including mental and non-mental health professionals, and non-health organisations (Fusar-Poli *et al*., 2013; Green *et al*., 2011). These teams attempt to respond to all referrals and conduct the first assessment within the first week of the referral being made. This is considerably shorter than most psychiatric services can offer. For those patients who are judged to meet criteria for the ARMS, the services provide a 2-3 year treatment plan (Green *et al*., 2011).

However, there is a question of whether individuals who contact the ARMS services and meet criteria for the ARMS are representative of all pre-psychotic individuals. For example, Ajnakina *et al*. (2017) showed that those with the ARMS, who attended an ARMS clinic in South-London and later developed clinical psychosis, were more likely than those FEP patients who had not attended such a clinic, to be born in the UK and have strong family support, with migrants being less likely to access the services. Others showed that the young people who met criteria for the ARMS and attended an ARMS clinic were likely to be employed and have higher educational achievements (Addington *et al*., 2012; Valmaggia *et al*., 2015).

The reason for such differences is likely to be that the ARMS services require individuals to be help-seeking. Migrants and ethnic minorities are well-known to be less trusting of mental health services than those from the host population (Morgan *et al*., 2006). Availability of supportive families and strong social networks, which are frequently absent in those with clinical psychotic illness (Sundermann *et al*., 2014), are also important factors for help-seeking (Morgan *et al*., 2006). Moreover, to recognise “not-quite-psychotic” symptoms, the potential patients, or their relatives, need to have some knowledge

of such symptoms plus insight into their potential illness significance. It is not surprising, therefore, that those patients who have been accepted under the care of the ARMS services have better insight compared to psychosis patients who do not reach these services (Lappin *et al*., 2007). Another reason why prodromal samples cannot be representative of all pre-psychotic individuals is that some patients present so acutely (Ajnakina *et al*., 2017) that even if they were willing to accept help there is no time to intervene (Shah *et al*., 2017). Therefore, the evidence suggests that under current pathway configurations, services for those who meet the criteria for the ARMS appear to attract a subgroup of pre-psychotic individuals who are atypical of all those people who will develop FEP. This in turn should raise some doubts as to whether some of the benefits claimed for ARMS clinics (Valmaggia *et al*., 2015) are actually a reflection of the population attracted to the ARMS clinics, rather than the care offered by the clinics. The nature of the unselected, representative and non-help seeking population samples remains unknown.

Have the transition rates fallen?

Early studies reported that 30-54% of those with the ARMS went on to develop full psychotic disorder in the following 12-24 months (Fusar-Poli *et al*., 2012; Miller *et al*., 2002; Yung *et al*., 2003). Some more recent reports, however, have suggested that the transition rates from the ARMS phase to clinical psychosis are as low as 8-17% within a 2-year period (Morrison *et al*., 2012; Carrion *et al*., 2016; Conrad *et al*., 2017; Malla *et al*., 2017). It is possible that the reduced reported transition rates may be an outcome of successful interventions implemented by ARMS clinics (McGorry *et al*., 2006; Nelson *et al*., 2016).

However, it is likely that the reduced estimated transition rates are, at least in part, a consequence of other factors such as changes in characteristics of the sample or their pathways to care (Wiltink *et al*., 2015) as well as different definitions of what constitutes transition to psychosis employed across studies (van Os and Guloksuz, 2017). Further, van

Os (2005) highlighted that the high positive predictive values presented by some studies when predicting the transition from the ARMS phase to clinical psychosis (Miller *et al*., 2002; Yung *et al*., 2003) are actually an outcome of the sample enrichment that results from the mainstream sample selection procedures. This in turn leads to spuriously increased incidence and predictive values (van Os, 2005). In fact, when the transition rate was estimated based on the actual prevalence of the ARMS in the general population it was shown to be around 1% (van Os, 2005).

Another important reason why transition rates are lower than previously reported may be that the identified pre-psychotic patients are diluted in more recent studies by large numbers of patients with other psychiatric problems. This may be due to referrers realising that the clinics provide an opportunity for a rapid clinical assessment of distressed young people. A recent review suggested that over 80% of individuals referred as “at risk for psychosis” will never develop clinical psychosis (van Os and Reininghaus, 2016). This raises ethical issues relating to medication exposure and stigma among those who were false-positives (Bentall and Morrison, 2002; McGlashan, 2001). Even for those individuals who were identified at UHR by the ARMS services, the evidence for effectiveness of the interventions that these prodromal clinics offer is weak (Castle, 2012).

Criticisms of the ARMS Concept

The assumption behind AMRS clinics is that the ARMS state is what van Os and Murray RM (2013) called a “schizophrenia light”: defined according to an (arbitrary) cut-off of psychosis severity or a (similarly arbitrary) diagnostic concept of “schizophrenia spectrum”. People can cross and re-cross this boundary several times (van Os and Murray, 2013). As the expression of psychosis naturally fluctuates in intensity and severity within individuals over time, temporary amelioration of psychosis at the time of the baseline assessment may cause these people to be wrongly assigned to the UHR group rather than the psychotic group.

Furthermore, psychotic symptoms are much more common than previously realised. Indeed, they are found in about 5% of the general population, 9% of adolescents, and 25% of people with (non-psychotic) common mental disorders (Linscott and Van Os, 2013; van Os and Reininghaus, 2016; Zammit *et al*., 2013). Interestingly, one study found that 16% of non-psychotic young people who were assessed and found not to meet the UHR criteria made a transition to clinical psychosis (Carr, 2012). These figures vary depending on different methods of data acquisition and categorisation (David, 2010). Thus, it is difficult to define with certainty when an individual transits from pre-psychotic symptoms to the ARMS, and at the other end from the ARMS to clinical psychosis (David and Ajnakina, 2016).

To further complicate matters, the symptoms that are at the core of the definition of the ARMS phase are frequently present in other mental disorders (Kelleher *et al*., 2012; van Os and Guloksuz, 2017). Studies of UHR groups show that they consist largely of people with common mental disorders such as anxiety and depression (Addington *et al*., 2017; Fusar-Poli *et al*., 2014). Therefore, the presence of psychotic symptoms in themselves should not be seen as an indication of the risk to making the transition to psychosis (Murray and Jones, 2012).

ARMS clinics are morphing into clinics for youth mental health

The realisation that the most common diagnoses reported in young people attending the ARMS clinics are anxiety, depression and personality disorders (Kelleher *et al*., 2012) prompted McGorry, one of the founders of the ARMS movement, to broaden the scope of such clinics from focussing on those at risk for psychosis to becoming more general outreach clinics for youth who are at risk for any mental disorders (Malla *et al*., 2016; McGorry *et al*., 2013). Thus, the idea of specific clinics for pre-psychotic individuals has been replaced with cross-diagnostic youth mental health facilities with much broader and more inclusive (and laudable) purpose of identifying and caring for young people with mental health problems (Malla *et al*.,

2016; McGorry *et al*., 2013). The inclusive concept of youth mental health is broad enough to encompass any potential abnormality and does not require being either severe or specific enough to warrant a clinical diagnosis. This approach has much to commend it but an early evaluation of such services in Australia foundthat evidence of benefit was inconclusive (Hilferty *et al*., 2015).

A Public Health Approach

Can prodromal clinics ever prevent development of clinical psychosis in a significant number of pre-psychotic individuals? Ajnakina *et al*. (2017) carried out a comprehensive evaluation of FEP patients in an area of South-London which has had a well-developed ARMS service for more than ten years serving the same catchment area. They found that only 4.1% of FEP patients had previously made contact with ARMS services and met the ARMS criteria (most presented to FEP psychosis directly or via other routes). This very low proportion suggests that the scope for ARMS services reducing or postponing the onset of psychosis is limited as is their public health or economic impact (van Os and Guloksuz, 2017).

We recognise, of course, that ARMS clinics have provided a valuable source of pre-psychotic patients for research. This in turn has ignited an explosion of research findings (Anticevic *et al*., 2015; Cannon *et al*., 2015; Walker *et al*., 2013). For example, it has been shown that individuals with the ARMS who proceed to develop clinical psychosis have an excess capacity to synthesise striatal dopamine (DA) which increases further as they get nearer to clinical psychosis, compared to healthy controls (Howes *et al*., 2011) and that cortical volume loss may be accelerated in the months prior to transition (Cannon *et al.,* 2015). Nonetheless, this does imply that the process of developing psychosis has already begun in people with the ARMS. Therefore, it reinforces the point that intervening at this stage may already be too late.

The development of ARMS clinics has also increased awareness of a greater opportunity for prevention and early intervention. In medicine, preventive approaches to illnesses such as heart disease, bronchitis, or obesity do not focus on identifying individuals just on the brink of developing the disorder or carrying biological markers for it. Instead, they target the known risk factors for the conditions, and encourage members of the general public to change their behaviour, for example start exercising or reduce calorie or cigarette intake, with the aim of reducing their risk of developing the condition.

A similar approach should be adopted for psychosis. Indeed, a number of risk factors for developing psychosis have been identified and replicated. These include obstetric events, childhood adversity, urban birth and upbringing, and adverse life events (Gaag *et al*., 2016; Radua *et al.,* 2018; Stilo and Murray, 2010). Moreover, a recent large and methodological rigorous study has provided further empirical evidence for the link between risk for psychosis onset and immigration (Jongsma *et al*., 2018).

The evidence that cannabis use is an important risk factor for later developing psychotic symptoms and/or psychotic disorder is especially strong (Murray *et al*., 2016). This risk has been shown to increase linearly with a greater frequency, longer length of use, and the stronger potency of the cannabis used (Di Forti *et al*., 2014; Marconi *et al*., 2016). Importantly, it has been demonstrated that a substantial proportion of first episode psychosis cases (24% in London) would have been prevented if no one consumed cannabis of high potency (Di Forti *et al*., 2015). The risk increasing effects of cannabis extend to individuals who meet criteria for ARMS, reiterating the importance of this risk factor for preventative purposes. Indeed, it has been reported that individuals meeting criteria for ARMS not only have high rates of cannabis use (Carney *et al*., 2017) but also that those who have used cannabis at least weekly have significantly more severe positive psychotic symptoms than non-cannabis users (Niemann *et al*., 2016).

In the long-term, attempts to reduce exposure to these risk factors for psychosis should be made. Though this will not be easy since the pathogenic mechanism underlying the link between some of these risk factors and psychosis is not yet understood; for example, it is likely that urban living is a proxy for one or more more specific psychotogenic factor(s). Furthermore, it may be very difficult to diminish exposure to some risk factors eg child abuse or migration. However, an obvious place to start is by attempting to reduce society's consumption of high-potency cannabis through public education (Gage *et al*., 2016; Di Forti *et al*., 2015). Unfortunately, the legalisation of cannabis for "medicinal" or "recreational" use across states of the USA has been accompanied by an increase in the use and potency of cannabis (Rehm and Fischer, 2015; Heslin et al, 2018). Thus, public policy in North America appears to be moving in the opposite direction. Psychiatrists need to be more vocal in drawing attention to the risks to mental health involved in policies which increase consumption of high potency cannabis.

Conclusion

The idea of identifying individuals before they become unwell is a worthy idea, especially in the era when our treatments for psychosis are far from perfect. However, it is clear that the task of making a major contribution to the prevention of psychosis is beyond the power of the ARMS clinics. A public health approach to prevention of psychosis has the potential to be more effective. Nonetheless, should such the ARMS clinic continue to exist, they face an important challenge in regard to developing pathways which will attract a broader and more representative group of individuals to access their services.

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Conflict of interest

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References:

Addington J, Cadenhead KS, Cornblatt BA, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Addington JA, Cannon TD (2012). North American Prodrome Longitudinal Study (NAPLS 2): overview and recruitment. *Schizophrenia Research* **142**, 77-82.

Addington J, Epstein I, Reynolds A, Furimsky I, Rudy L, Mancini B, McMillan S, Kirsopp D, Zipursky RB (2008). Early detection of psychosis: finding those at clinical high risk. *Early Intervention in Psychiatry* **2**, 147-53.

Addington J, Piskulic D, Liu L, Lockwood J, Cadenhead KS, Cannon TD, Cornblatt BA, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Bearden CE, Mathalon DH, Woods SW (2017). Comorbid diagnoses for youth at clinical high risk of psychosis. *Schizophrenia Research* **190**, 90-95.

Ajnakina O, Morgan C, Gayer-Anderson C, Oduola S, Bourque F, Bramley S, Williamson J, MacCabe JH, Dazzan P, Murray RM, David AS (2017). Only a small proportion of patients with first episode psychosis come via prodromal services: a retrospective survey of a large UK mental health programme. *BMC Psychiatry* **17**, 017-1468.

Anticevic A, Haut K, Murray JD, Repovs G, Yang GJ, Diehl C, McEwen SC, Bearden CE, Addington J, Goodyear B, Cadenhead KS, Mirzakhanian H, Cornblatt BA, Olvet D, Mathalon DH, McGlashan TH, Perkins DO, Belger A, Seidman LJ, Tsuang MT, van Erp TG, Walker EF, Hamann S, Woods SW, Qiu M, Cannon TD (2015). Association of Thalamic Dysconnectivity and Conversion to Psychosis in Youth and Young Adults at Elevated Clinical Risk. *JAMA Psychiatry*, **72**, 882-91

Bentall RP & Morrison AP (2002). More harm than good: The case against using antipsychotic drugs to prevent severe mental illness. *Journal of Mental Health* **11**, 351-356.

Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R; North American Prodrome Longitudinal Study Consortium (2015). Progressive Reduction in Cortical Thickness as Psychosis Develops: A Multisite Longitudinal Neuroimaging Study of Youth at Elevated Clinical Risk. *Biological Psychiatry* **77**, 147-57.

Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TGM, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R, on behalf of the North American Prodrome Longitudinal Study Consortium (2015). Progressive Reduction

in Cortical Thickness as Psychosis Develops: A Multisite Longitudinal Neuroimaging Study of Youth at Elevated Clinical Risk. *Biological Psychiatry* **77**, 147–15

Cannon TD, Yu C, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, Heinssen R, Jeffries CD, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Kattan MW (2016). An Individualized Risk Calculator for Research in Prodromal Psychosis. *American Journal of Psychiatry* **173**, 980-988.

Carney R, Cotter J, Firth J, Bradshaw T, Yung AR (2017). Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis. *Acta Psychiatrica Scandinavica* **136**, 5-15.

Carr V (2012). Time to move on? Commentary on the early intervention in psychosis debate. *Australian and New Zealand Journal of Psychiatry* **46**, 384-386.

Carrion RE, Cornblatt BA, Burton CZ, Tso IF, Auther AM, Adelsheim S, Calkins R, Carter CS, Niendam T, Sale TG, Taylor SF, McFarlane WR (2016). Personalized Prediction of Psychosis: External Validation of the NAPLS-2 Psychosis Risk Calculator With the EDIPPP Project. *American Journal of Psychiatry* **173**, 989-996.

Castle DJ (2012). Is it appropriate to treat people at high-risk of psychosis before first onset? - no. *Medical Journal of Australia* **196**, 557.

Conrad AM, Lewin TJ, Sly KA, Schall U, Halpin SA, Hunter M, Carr VJ (2017). Utility of risk-status for predicting psychosis and related outcomes: evaluation of a 10-year cohort of presenters to a specialised early psychosis community mental health service. *Psychiatry Research* **247**, 336-344.

Corcoran CM, First MB, Cornblatt B (2010). The psychosis risk syndrome and its proposed inclusion in the DSM-V: a risk-benefit analysis. *Schizophrenia Research* **120**, 16-22.

Craig TK, Garety P, Power P, Rahaman N, Colbert S, Fornells-Ambrojo M, Dunn G. (2004). The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ* **329**: 1067

David AS & Ajnakina O (2016). Psychosis as a continuous phenotype in the general population: the thin line between normality and pathology. *World Psychiatry* **15**, 129-30.

David AS (2010). Why we need more debate on whether psychotic symptoms lie on a continuum with normality. *Psychological Medicine* **40**, 1935-42.

Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, Bianconi F, Gardner-Sood P, O'Connor J, Russo M, Stilo SA, Marques TR, Mondelli V, Dazzan P, Pariante C., David AS, Gaughran F, Atakan Z, Iyegbe C, Powell J, Morgan C, Lynskey M & Murray, RM (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry* **2**, 233-8.

Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, Marconi A, La Cascia C, Reis Marques T, Pariante C, Dazzan P, Mondelli V, Paparelli A, Kolliakou A, Prata D, Gaughran F, David AS, Morgan C, Stahl D, Khondoker M, MacCabe JH & Murray RM (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin* **40**, 1509-17.

Falloon IR (1992). Early intervention for first episodes of schizophrenia: a preliminary exploration. P*sychiatry* **55**, 4-15.

Falloon IR, Kydd RR, Coverdale JH, Laidlaw TM (1996). Early detection and intervention for initial episodes of schizophrenia. *Schizophrenia Bulletin* **22**, 271-82.

Frances A (2009). Whither DSM-V? *British Journal of Psychiatry* **195**, 391-2.

345 **Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F,**
346 **Caverzasi E, McGuire P** (2012). Predicting psychosis: meta-analysis of transition outcomes
347 in individuals at high clinical risk. *Archives of General Psychiatry* **69**, 220-9.

348 **Fusar-Poli P, Byrne M, Badger S, Valmaggia LR, McGuire PK** (2013). Outreach and
349 support in south London (OASIS), 2001-2011: ten years of early diagnosis and treatment for
350 young individuals at high clinical risk for psychosis. *European Psychiatry* **28**, 315-26.

351 **Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire P** (2014). Comorbid depressive
352 and anxiety disorders in 509 individuals with an at-risk mental state: impact on
353 psychopathology and transition to psychosis. *Schizophrenia Bulletin* **40**, 120-131.

354 **Gage SH, Hickman M, Zammit S** (2016). Association between cannabis and psychosis:
355 epidemiologic evidence. *Biological Psychiatry* **79**, 549-56.

356 **Green CE, McGuire PK, Ashworth M, Valmaggia LR** (2011). Outreach and Support in South
357 London (OASIS). Outcomes of non-attenders to a service for people at high risk of psychosis:
358 the case for a more assertive approach to assessment. *Psychological Medicine* **41**, 243-50.

359 **Hastrup LH, Kronborg C, Bertelsen M, Jeppesen P, Jorgensen P, Petersen L, Thorup A,**
360 **Simonsen E, Nordentoft M** (2013). Cost-effectiveness of early intervention in first-episode
361 psychosis: economic evaluation of a randomised controlled trial (the OPUS study). *British*
362 *Journal of Psychiatry* **202**, 35-41

363 **Hilferty F, Cassells R, Muir K, Duncan A, Christensen D, Mitrou F, Gao G, Mavisakalyan**
364 **A, Hafekost K, Tarverdi Y, Nguyen H, Wingrove C, and Katz I** (2015). *Is headspace making*
365 *a difference to young people's lives? Final Report of the independent evaluation of the*
366 *headspace program*. (SPRC Report 08/2015). Sydney: Social Policy Research Centre, UNSW
367 Australia.

Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D, Valmaggia L, Allen P, Murray R, McGuire P (2011) Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Molecular Psychiatry* **16**, 885-6.

Jongsma HE, Gayer-Anderson C, Lasalvia A, Quattrone D, Mulè A, Szöke A, Selten J-P, Turner C, Arango C, Tarricone I, Berardi D, Tortelli A, Llorca PM, de Haan L, Bobes J, Bernardo D, Sanjuán J, Santos JL, Arrojo J, Del-Ben CM, Menezes P, Velthorst E, Murray RM, Rutten BP, Jones PB, van Os J, Morgan C, and Kirkbride J (2018). Treated incidence of psychotic disorders in the multinational EU-GEI study. *JAMA Psychiatry* **75**, 36-46.

Kelleher I, Murtagh A, Molloy C, Roddy S, Clarke MC, Harley M, Cannon M (2012). Identification and characterization of prodromal risk syndromes in young adolescents in the community: a population-based clinical interview study. *Schizophrenia Bulletin* **38**, 239-46.

Killackey E & Yung AR (2007). Effectiveness of early intervention in psychosis. *Current Opinion in Psychiatry* **20**, 121-5.

Lappin JM, Morgan KD, Valmaggia LR, Broome MR, Woolley JB, Johns LC, Tabraham P, Bramon E, McGuire PK (2007). Insight in individuals with an At Risk Mental State. *Schizophrenia Research* **90**, 238-44.

Linscott RJ, Van Os J (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine* **43**, 1133-49.

Loewy RL, Pearson R, Vinogradov S, Bearden CE, Cannon TD (2011). Psychosis risk screening with the Prodromal Questionnaire--brief version (PQ-B). *Schizophrenia Research* **129**, 42-6.

Malla A, de Bonneville M, Shah J, Jordan G, Pruessner M, Faridi K, Rabinovitch M, Iyer SN, Joober R (2017). Outcome in patients converting to psychosis following a treated clinical high risk state. *Early Intervention Psychiatry* **14**, 12431.

Malla A, Iyer S, McGorry P, Cannon M, Coughlan H, Singh S, Jones P, Joober R. (2016). From early intervention in psychosis to youth mental health reform: a review of the evolution and transformation of mental health services for young people. *Social Psychiatry and Psychiatric Epidemiology* **51**, 319-26.

Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* **42**, 1262–1269.

McGlashan TH (2001). Psychosis treatment prior to psychosis onset: ethical issues. *Schizophrenia Research* **51**, 47-54.

McGorry P, Bates T, Birchwood M (2013). Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. *British Journal of Psychiatry. Supplement* **54**, 119214.

McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ (2006). Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Australian and New Zealand Journal of Psychiatry* **40**, 616-22.

Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry* **159**, 863-865.

Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW (2003). Prodromal assessment with the structured

interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin* **29**, 703–715.

Morgan C, Abdul-Al R, Lappin JM, Jones P, Fearon P, Leese M, Croudace T, Morgan K, Dazzan P, Craig T, Leff J, Murray R (2006). Clinical and social determinants of duration of untreated psychosis in the AESOP first-episode psychosis study. *British Journal of Psychiatry* **189**, 446-52.

Morrison AP, French P, Stewart SL, Birchwood M, Fowler D, Gumley AI, Jones PB, Bentall RP, Lewis SW, Murray GK, Patterson P, Brunet K, Conroy J, Parker S, Reilly T, Byrne R, Davies LM, Dunn G. (2012). Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *BMJ* **344**, e2233. doi: 10.1136/bmj.e2233.

Murray GK, Jones PB (2012). Psychotic symptoms in young people without psychotic illness: mechanisms and meaning. *British Journal of Psychiatry* **201**, 4-6.

Murray RM, Quigley H, Quattrone S, Englund A, Di Forti M (2016). Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry* **15**, 195–204.

Nelson B, Yuen HP, Lin A, Wood SJ, McGorry PD, Hartmann JA, Yung AR (2016). Further examination of the reducing transition rate in ultra high risk for psychosis samples: The possible role of earlier intervention. *Schizophrenia Research* **174**, 43-9.

Nieman DH, Dragt S, van Duin EDA, Denneman N, Overbeek JM, de Haan L, Rietdijk J, Ising HK, Klaassen RMC, van Amelsvoort T, Wunderink L, van der Gaag M, Linszen DH (2016). COMT Val158Met genotype and cannabis use in people with an At Risk Mental State for psychosis: Exploring Gene x Environment interactions. *Schizophrenia Research*, **174**, 24-28

Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, Yenn Thoo H, Oliver D, Davies C, Morgan C, McGuire P, Murray RM, Fusar-Poli P (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry* **17**, 49-66.

Reddy MS (2014). Attenuated psychosis syndrome. *Indian Journal of Psychological Medicine* **36**, 1-3.

Rehm, J. and Fischer, B (2015). Cannabis Legalization With Strict Regulation, the Overall Superior Policy Option for Public Health. *Clinical pharmacology & therapeutics* **97**, 541-544.

Stilo SA and Murray RM (2010). The epidemiology of schizophrenia. *Dialogues in Clinical Neuroscience* **12**, 305-315

Sundermann O, Onwumere J, Kane F, Morgan C, Kuipers E (2014). Social networks and support in first-episode psychosis: exploring the role of loneliness and anxiety. *Social Psychiatry Psychiatr Epidemiology* **49**, 359-366

Valmaggia LR, Byrne M, Day F, Broome MR, Johns L, Howes O, Power P, Badger S, Fusar-Poli P, McGuire PK (2015). Duration of untreated psychosis and need for admission in patients who engage with mental health services in the prodromal phase. *British Journal of Psychiatry* **207**, 130-4.

van Os J & Murray RM (2013). Can we identify and treat "schizophrenia light" to prevent true psychotic illness? *BMJ* **18**, 346.

van Os J & Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* **15**, 118-24.

van Os, J (2005). Toward a world consensus on prevention of schizophrenia. *Dialogues in Clinical Neuroscience* **7**, 53–67.

van Os, J and Guloksuz S (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* **16**, 200-206.

Walker EF, Trotman HD, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA, Heinssen R, Mathalon DH, Perkins DO, Seidman LJ, Tsuang MT, Cannon TD, McGlashan TH, Woods SW (2013). Cortisol Levels and Risk for Psychosis: Initial Findings from the North American Prodrome Longitudinal Study. *Biological Psychiatry* **74**, 410-7

Wiltink S, Velthorst E, Nelson, B, McGorry PM, Yung AR (2015). Declining transition rates to psychosis: the contribution of potential changes in referral pathways to an ultra-high-risk service. *Early Intervention in Psychiatry* **9**, 200-206.

Wood SJ, Reniers RL & Heinze K (2013). Neuroimaging findings in the at-risk mental state: a review of recent literature. *Canadian Journal of Psychiatry* **58**, 13-8.

Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH (2009). Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophrenia Bulletin* **35**, 894–908.

Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A (1996). Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin* **22**, 283-303.

Yung AR, Nelson B, Stanford C, Simmons MB, Cosgrave EM, Killackey E, Phillips LJ, Bechdolf A, Buckby J, McGorry PD (2008). Validation of “prodromal” criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophrenia Research* **105**, 10-17.

Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD (2003). Psychosis prediction: 12-month follow-up of a high-risk (“prodromal”) group. *Schizophrenia Research* **60**, 21-32.

Yung AR, Stanford C, Cosgrave E, Killackey E, Phillips L, Nelson B, McGorry PD (2006). Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophrenia Research* **84**, 57-66.

Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M, Francey SM, Cosgrave E. M, Killackey E, Stanford C, Godfrey K, Buckby J (2005). Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Australian and New Zealand Journal of Psychiatry* **39**, 964-71.

Zammit S, Kounali D, Cannon M, David AS, Gunnell D, Heron J, Jones PB, Lewis S, Sullivan S, Wolke D, Lewis G (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry* **170**, 742-50.